

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

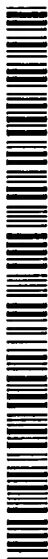


(43) International Publication Date
2 May 2002 (02.05.2002)

PCT

(10) International Publication Number
WO 02/34300 A1

- (51) International Patent Classification⁷: **A61K 51/06**,
A61P 35/00 Nathaniel [AU/AU]; 18 Riley Road, Claremont, Western
Australia 6010 (AU).
- (21) International Application Number: PCT/AU01/01370 (74) Agents: **SLATTERY, John, M.** et al.; Davies Collison
Cave, 1 Little Collins Street, Melbourne, Victoria 3000
(AU).
- (22) International Filing Date: 25 October 2001 (25.10.2001)
- (25) Filing Language: English (81) Designated States (*national*): AU, CA, JP, US.
- (26) Publication Language: English (84) Designated States (*regional*): European patent (AT, BE,
CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC,
NL, PT, SE, TR).
- (30) Priority Data:
PR 0983 25 October 2000 (25.10.2000) AU
- (71) Applicant (*for all designated States except US*): **SIRTEX
MEDICAL LIMITED** [AU/AU]; 125 Burswood Road,
Burswood, Western Australia 6100 (AU). **Published:**
— *with international search report*
- (72) Inventor; and *For two-letter codes and other abbreviations, refer to the "Guid-*
ance Notes on Codes and Abbreviations" appearing at the begin-
(75) Inventor/Applicant (*for US only*): **GRAY, Bruce**, *ning of each regular issue of the PCT Gazette.*



WO 02/34300 A1

(54) Title: POLYMER BASED RADIONUCLIDE CONTAINING PARTICULATE MATERIAL

(57) Abstract: The invention relates to a particulate material having a diameter in the range of from 5 to 200 microns comprising a polymeric matrix and stably incorporated radionuclide, processes for its production and a method of radiation therapy utilising the particulate material.

POLYMER BASED RADIONUCLIDE CONTAINING PARTICULATE MATERIAL

FIELD OF THE INVENTION

- 5 This invention relates to a particulate material that comprises a polymer, particularly a polymer and a radionuclide, to a method for the production thereof, and to methods for the use of this particulate material.

In one particular aspect, this invention relates to microspheres which comprise a polymer and a radionuclide such as radioactive yttrium, and to the use of these microspheres in the
10 treatment of cancer in humans and other mammals.

The particulate material of this invention is designed to be administered into the arterial blood supply of an organ to be treated, whereby it becomes entrapped in the small blood vessels of the target organ and irradiates it. An alternate form of administration is to inject the polymer based particulate material directly into the target organ or a solid tumour to be treated.

- 15 The particulate material of the present invention therefore has utility in the treatment of various forms of cancer and tumours, but particularly in the treatment of primary and secondary cancer of the liver and the brain. It is to be understood that the particulate material of the invention is not limited to radioactive microspheres, but may be extended to other radioactive polymeric particles which are suitable for use in the treatment methods described
20 herein.

BACKGROUND OF THE INVENTION

- Many previous attempts have been made to locally administer radioactive materials to patients with cancer as a form of therapy. In some of these, the radioactive materials have been
25 incorporated into small particles, seeds, wires and similar related configurations that can be directly implanted into the cancer. When radioactive particles are administered into the blood

-2-

supply of the target organ, the technique has become known as Selective Internal Radiation Therapy (SIRT). Generally, the main form of application of SIRT has been its use to treat cancers in the liver.

There are many potential advantages of SIRT over conventional, external beam radiotherapy.

- 5 Firstly, the radiation is delivered preferentially to the cancer within the target organ. Secondly, the radiation is slowly and continually delivered as the radionuclide decays. Thirdly, by manipulating the arterial blood supply with vasoactive substances (such as Angiotensin-2), it is possible to enhance the percentage of radioactive particles that go to the cancerous part of the organ, as opposed to the healthy normal tissues. This has the effect of
- 10 preferentially increasing the radiation dose to the cancer while maintaining the radiation dose to the normal tissues at a lower level (Burton, M.A. et al.; Effect of Angiotensin-2 on blood flow in the transplanted sheep squamous cell carcinoma. *Europ. J. Cancer Clin. Oncol.* 1988, 24(8):1373-1376).

- When microspheres or other small particles are administered into the arterial blood supply of
- 15 a target organ, it is desirable to have them of a size, shape and density that results in the optimal homogeneous distribution within the target organ. If the microspheres or small particles do not distribute evenly, and as a function of the absolute arterial blood flow, then they may accumulate in excessive numbers in some areas and cause focal areas of excessive radiation. It has been shown that microspheres of approximately 25-50 micron in diameter
- 20 have the best distribution characteristics when administered into the arterial circulation of the liver (Meade, V. et al.; Distribution of different sized microspheres in experimental hepatic tumours. *Europ. J. Cancer & Clin. Oncol.* 1987, 23:23-41).

- If the particles are too dense or heavy, then they will not distribute evenly in the target organ and will accumulate in excessive concentrations in areas that do not contain the cancer. It has
- 25 been shown that solid, heavy microspheres distribute poorly within the parenchyma of the liver when injected into the arterial supply of the liver. This, in turn, decreases the effective radiation reaching the cancer in the target organ, which decreases the ability of the radioactive microspheres to kill the tumour cells. In contrast, lighter microspheres with a specific gravity of the order of 2.0 distribute well within the liver (Burton, M.A. et al.; Selective International

Radiation Therapy; Distribution of radiation in the liver. Europ. J. Cancer Clin. Oncol. 1989, 25:1487-1491).

For radioactive particulate material to be used successfully for the treatment of cancer, the radiation emitted should be of high energy and short range. This ensures that the energy emitted will be deposited into the tissues immediately around the particulate material and not into tissues which are not the target of the radiation treatment. In this treatment mode, it is desirable to have high energy but short penetration beta-radiation which will confine the radiation effects to the immediate vicinity of the particulate material. There are many radionuclides that can be incorporated into microspheres that can be used for SIRT. Of particular suitability for use in this form of treatment is the unstable isotope of yttrium (Y-90).

Yttrium-90 decays with a half life of 64 hours, while emitting a high energy pure beta radiation. However, other radionuclides may also be used in place of yttrium-90 of which the isotopes of holmium, samarium, iodine, iridium, phosphorus, rhenium are some examples.

Ceramic particles have been produced that are either coated with or contain radionuclides. However, the presence of other radioactive substances that are not required for the radiation treatment of the target tissue, has then unwanted and deleterious radiation effects may occur. It is therefore desirable to have particulate material of such a composition that it only contains the single desired radionuclide.

In the earliest clinical use of yttrium-90 containing microspheres, the yttrium was incorporated into a polymeric matrix that was formulated into microspheres. While these microspheres were of an appropriate density to ensure good distribution characteristics in the liver, there were several instances in which the yttrium-90 leached from the microspheres and caused inappropriate radiation of other tissues. Attempts to incorporate other radionuclides such as holmium into resin or polymer based materials have resulted in leaching of the radionuclide and this has resulted in severe consequences for the patients that have been treated with the product.

In one attempt to overcome the problem of leaching, a radioactive microsphere comprising a biologically compatible glass material containing a beta- or gamma-radiation emitting

-4-

radioisotope such as yttrium-90 distributed throughout the glass, has been developed (International Patent Publication No. WO 86/03124). These microspheres are solid glass and contain the element yttrium-89 that can be activated to the radionuclide yttrium-90 by placing the microspheres in a neutron beam. These glass microspheres have several disadvantages including being of a higher specific gravity than is desirable and containing other elements such as alumina and silica which are activated to undesirable radionuclides when placed in a neutron beam.

Another approach has been focussed on the use of small hollow or cup-shaped ceramic particles or microspheres, wherein the ceramic base material consists or comprises yttria or the like (International Patent Publication No. WO 95/19841). These microspheres were developed to overcome the problem of high density associated with the solid glass microspheres described in International Patent Publication No. WO86/03124.

SUMMARY OF THE INVENTION

In one aspect the present invention provides a particulate material having a diameter in the range of from 5 to 200 microns comprising a polymeric matrix and a stably incorporated radionuclide.

In another aspect, the invention provides a process for the production of a particulate material having a diameter in the range of from 5 to 200 microns comprising the step of combining a polymeric matrix and a radionuclide for a time and under conditions sufficient to stably incorporate the radionuclide in the matrix to produce a particulate material having a diameter in the range of from 5 to 200 microns.

In another aspect, the present invention provides a method of radiation therapy of a patient, which comprises administration to the patient of a particulate material having a diameter in the range of from 5 to 200 microns comprising a polymeric matrix and a stably incorporated radionuclide.

-5-

The present invention also provides for the use of particulate material having a diameter in the range of from 5 to 200 microns comprising a polymeric matrix and a stably incorporated radionuclide in the radiation therapy of a patient.

5 DETAILED DESCRIPTION OF THE INVENTION

As used herein, references to the radionuclide being stably incorporated into particulate material or polymeric matrix are to be understood as referring to incorporation of the radionuclide so that it does not substantially leach out of the particulate material under physiological conditions such as in the patient or in storage. In a preferred embodiment the
10 radionuclide is incorporated by precipitation into a polymeric matrix.

The leaching of radionuclides from the polymeric matrix can cause non-specific radiation of the patient and damage surrounding tissue. Preferably the amount of leaching is less than 5%, more preferably less than 4%, 3%, 2%, 1% or 0.4%. One method of assessing leaching is by adjusting a sample to pH 7.0 and agitating in a water bath at 37°C for 20 minutes. A 100 µL
15 sample is counted for beta emission in a Geiger-Müller counter. Another representative 100 µL sample is filtered through a 0.22 µm filter and the filtrate counted for beta emission in the Geiger-Müller counter. The per cent unbound radionuclide is calculated by:

$$\frac{\text{FiltrateCount}}{\text{SampleCount}} \times 100 = \% \text{ UnboundRadionuclide}$$

The radionuclide can be stably incorporated into the polymeric matrix by precipitating it as an
20 insoluble salt. Where the radionuclide used is yttrium-90 the yttrium is preferably precipitated as a phosphate salt. However the present invention also extends to precipitation of the radionuclide as other insoluble salts including, for example, carbonate and bicarbonate salts. The radionuclide which is incorporated into the polymeric matrix in accordance with the present invention is preferably yttrium-90, but may also be any other suitable radionuclide
25 which can be precipitated in solution, of which the isotopes of holmium, samarium, iodine, phosphorous, iridium and rhenium are some examples.

-6-

In a preferred embodiment the particulate material is a microsphere. The term microsphere is used in this specification as an example of a particulate material, it is not intended to limit the invention to microspheres, as the person skilled in the art will appreciate that the shape of the particulate material while preferably without sharp edges or points that could damage the patients arteries or catch in unintended locations, is not limited to spheres. Nor should the term microsphere be limited to spheres. Preferably the particulate material is substantially spherical, but need not be regular or symmetrical in shape.

In a preferred embodiment the polymeric matrix is partially cross linked. Preferably there is about 1% to about 20% cross linking, preferably about 2% to 10% cross linking and more preferably about 4% cross linking.

In particular, the present invention provides a particulate material as described above in which the polymeric matrix is an ion exchange resin, particularly a cation exchange resin. Preferably the ion exchange resin comprises a partially cross linked aliphatic polymer, including polystyrene. One particularly preferred cation exchange resin is the styrene/divinylbenzene copolymer resin commercially available under the trade name Aminex 50W-X4 (Biorad, Hercules, CA). However, there are many other commercially available cation exchange resins which are suitable.

When small particles are administered into the arterial blood supply of a target organ, it is desirable to have them of a size, shape and density that results in the optimal homogeneous distribution within the target organ. If the small particles do not distribute evenly then they may accumulate in excessive numbers in some areas and cause focal areas of excessive radiation. The particulate material is preferably low density, more particularly a density below 3.0 g/cc, even more preferably below 2.8g/cc, 2.5g/cc, 2.3g/cc, 2.2g/cc or 2.0 g/cc. The ideal particle for injection into the blood stream would have a very narrow size range with a SD of less than 5%, so as to assist in even distribution of the microspheres within the target organ, particularly within the liver and would be sized in the range 5-200 micron preferably 15-100 micron and preferably 20-50 micron, and most preferably 30-35 micron.

It is also desirable to have the particulate material manufactured so that the suspending

-7-

solution has a pH less than 9. If the pH is greater than 9 then this may result in irritation of the blood vessels when the suspension is injected into the artery or target organ. Preferably the pH is less than 8.5 or 8.0 and more preferably less than 7.5.

The present invention particularly provides a method for the production of a radioactive
5 particulate material comprising a polymeric matrix as described above, characterised by the steps of:

- (i) absorbing a radionuclide onto an ion-exchange resin particulate material having a diameter in the range of 20 to 50 microns and a specific gravity of less than 2.5; and
- (ii) precipitating the radionuclide as an insoluble salt to stably incorporate the radionuclide
10 into the particulate material.

In a preferred embodiment, the method of the present invention is carried out by firstly irradiating yttria (yttrium oxide) in a neutron beam to activate yttria to the isotope yttrium-90.

The yttrium-90 oxide is then solubilised, for example as yttrium-90 sulphate solution. The ion exchange resin is preferably provided in the form of an aqueous slurry of microspheres of
15 ion exchange resin having a particle size 30 to 35 microns, and the yttrium-90 sulphate solution is added to the slurry to absorb the yttrium-90 into the ion exchange resin microspheres. Subsequently, the yttrium-90 is precipitated as a phosphate salt, for example by addition of tri-sodium phosphate solution, to stably incorporate the yttrium-90 into the microspheres. The particulate material may be combined with a solution of the radionuclide
20 or the salt of the radionuclide may be combined with the particulate matter, in a solution suitable for solubilising the radionuclide.

Alternate sources of yttrium-90 may be used in the production of these microspheres. For example, a highly pure source of yttrium-90 may be obtained by extracting yttrium-90 from a parent nuclide and using this extracted yttrium-90 as the source of the soluble yttrium salt
25 that is then incorporated into the polymeric matrix of the microspheres.

In order to decrease the pH of the suspension containing the microspheres for injection into patients the microspheres may be washed to remove any un-precipitated or loosely adherent

-8-

radionuclide. The present invention provides a suspension of the required pH by precipitating the yttrium with a tri-sodium phosphate solution at a concentration containing at least a three-fold excess of phosphate ion, but not exceeding a 30-fold excess of phosphate ion, and then washing the microspheres with de-ionised water. Another approach which ensures that the pH
5 of the microsphere suspension is in the desired range is to wash the resin with a phosphate buffer solution of the desired pH.

The present invention also provides a method of radiation therapy of a human or other mammalian patient that comprises administration to the patient of particulate material as described above. The person skilled in the art will appreciate the administration may be by any
10 suitable means and preferably by delivery to the relevant artery. For example in treating liver cancer, administration is preferably by laparotomy to expose the hepatic artery or by insertion of a catheter into the hepatic artery via the femoral, or brachial artery. Pre or co-administration of another agent may prepare the tumour for receipt of the particulate material, for example a vasoactive substance, such as angiotension-2 to redirect arterial blood flow into the tumour.
15 Delivery of the particulate matter may be by single or multiple doses, until the desired level of radiation is reached.

Throughout this specification, unless the context requires otherwise, the word "comprise", and or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other
20 integer or step or group of integers or steps.

Further features of the present invention are more fully described in the following Examples. It is to be understood, however, that this detailed description is included solely for the purposes of exemplifying the present invention, and should not be understood in any way as a restriction on the broad description of the invention as set out above.

25

EXAMPLE 1

Yttrium (90Y) labelled microspheres are made in the form of a sterile, pyrogen free suspension

-9-

of resin beads labelled with yttrium (90Y) phosphate. The resin beads consist of sulphuric acid groups attached to a styrene divinylbenzene copolymer lattice.

Yttrium oxide is irradiated to produce yttrium-90 from the nuclear reaction $Y-89 (n, \gamma) Y-90$.

Yttrium-90 has a half life of 64 hours. The yttrium (90Y) oxide is then dissolved in 0.1M
5 sulphuric acid with gentle heating and stirring to form a clear, colourless solution of yttrium (90Y) sulphate.

Symmetrical microspheres of ion exchange resin (Aminex 50W-X4 cation exchange resin; supplied by 'Bio-Rad Cat # 1474313') with a diameter of approximately 30 to 35 microns are added to water (Water for Injections BP) to form a slurry that is then transferred into a reaction
10 vessel. Yttrium (90Y) sulphate solution is added to the reaction vessel and the mixture stirred at a speed sufficient to ensure homogeneity to absorb the yttrium (90Y) solution into the resin-based microspheres. Tri-sodium phosphate solution (1.25% w/v) is then added to the reaction vessel with further stirring to precipitate the radionuclide as yttrium (90Y) phosphate.

The microspheres are then washed with a phosphate buffer solution until the pH of the wash
15 solution is less than 9 and preferable less than 8.5. Following washing of the microspheres with water (Water for Injection BP), the microspheres are resuspended and diluted (if necessary) with water (Water for Injections BP) to give a light brown suspension having an activity of 3000 MBq \pm 10%.

The resin-based yttrium microspheres produced by the above method have 0.01-0.4% unbound
20 or unprecipitated 90Y when tested in the following leaching test:

A 5 μ L sample is diluted with water to 5 mL, adjusted to pH 7.0 and agitated in a water bath at 37°C for 20 minutes. A 100 μ L sample is counted for beta emission in a Geiger-Müller counter. Another representative 100 μ L sample is filtered through a 0.22 μ m filter and the filtrate counted for beta emission in the Geiger-Müller counter. The per cent unbound 90Y
25 is calculated by:

$$\frac{\text{FiltrateCount}}{\text{SampleCount}} \times 100 = \% \text{Unbound}^{90} \text{Y}$$

EXAMPLE 2

The effect of phosphate concentration in the precipitation solution, and the effects of washing with phosphate buffer on the pH of a microsphere suspension are shown in the attached Figure 1 which sets out the results of a number of experiments.

EXAMPLE 3

The technique of Selective Internal Radiation Therapy (SIRT) has been described above. It involves either a laparotomy to expose the hepatic arterial circulation or the insertion of a catheter into the hepatic artery via the femoral, brachial or other suitable artery. This may be followed by the infusion of Angiotensin-2 into the hepatic artery to redirect arterial blood to flow into the metastatic tumour component of the liver and away from the normal parenchyma. This is followed by embolisation of resin based yttrium-90 containing microspheres (produced in accordance with Example 1) into the arterial circulation so that they become lodged in the microcirculation of the tumour. Repeated injections of microspheres are made until the desired radiation level in the normal liver parenchyma is reached. By way of example, an amount of yttrium-90 activity that will result in an inferred radiation dose to the normal liver of approximately 80 Gy may be delivered. Because the radiation from SIRT is delivered as a series of discrete point sources, the dose of 80 Gy is an average dose with many normal liver parenchymal cells receiving much less than that dose.

The measurement of tumour response by objective parameters including reduction in tumour volume and serial estimations of serum carcino-embryonic antigen (CEA) levels, is an acceptable index of the ability of the treatment to alter the biological behaviour of the tumour.

CLAIMS:

1. A particulate material having a diameter in the range of from 5 to 200 microns comprising a polymeric matrix and stably incorporated radionuclide.
2. The particulate material according to claim 1 wherein the radionuclide is incorporated by precipitation.
3. The particulate material according to claim 1 wherein the polymeric matrix is partially cross linked.
4. The particulate material according to claim 3 wherein the polymeric matrix comprises from about 1% to about 20% cross linking.
5. The particulate material according to claim 4 wherein the polymeric matrix comprises about 4% cross linking.
6. The particulate material according to claim 1 wherein the polymeric matrix is an ion exchange resin.
7. The particulate material according to claim 6 wherein the polymeric matrix is a cation exchange resin.
8. The particulate material according to claim 6 wherein the ion exchange resin comprises a partially cross linked aliphatic polymer.
9. The particulate material according to claim 6 wherein the ion exchange resin comprises a partially cross linked polystyrene.
10. The particulate material according to claim 9 wherein the ion exchange resin comprises polystyrene partially cross linked with divinyl benzene.
11. The particulate material according to claim 1, wherein the radionuclide is an isotope of yttrium, holmium, samarium, iodine, phosphorus, iridium or rhenium.

-12-

12. The particulate material according to claim 1, wherein the radionuclide is yttrium-90.
13. The particulate material according to claim 1 being a microsphere.
14. A particulate material having a diameter in the range of from 30 to 35 microns comprising a copolymer comprised of styrene and divinyl benzene and precipitated yttrium-90.
15. A process for the production of a particulate material according to claim 1 comprising the step of combining a polymeric matrix and a radionuclide in solution for a time and under conditions sufficient to stably incorporate the radionuclide in the matrix to produce a particulate material having a diameter in the range of from 5 to 200 microns.
16. A process according to claim 15 wherein the radionuclide is stably incorporated by precipitation into the polymeric matrix.
17. A process according to claim 15 wherein the radionuclide is yttrium-90.
18. A method of radiation therapy of a patient, which comprises administration to the patient of a particulate material having a diameter in the range of from 5 to 200 microns comprising a polymeric matrix and a stably incorporated radionuclide.
19. A method according to claim 18 wherein the radionuclide is yttrium-90.
20. A method according to claim 18 wherein the radiation therapy comprises treatment of a primary or secondary liver cancer.
21. Use of particulate material having a diameter in the range of from 5 to 200 microns comprising a polymeric matrix and a stably incorporated radionuclide in radiation therapy of a patient.
22. Use according to claim 21 wherein the radionuclide is yttrium-90.
23. Use according to claim 21 wherein the radiation therapy comprises treatment of a primary or secondary liver cancer.

1/1

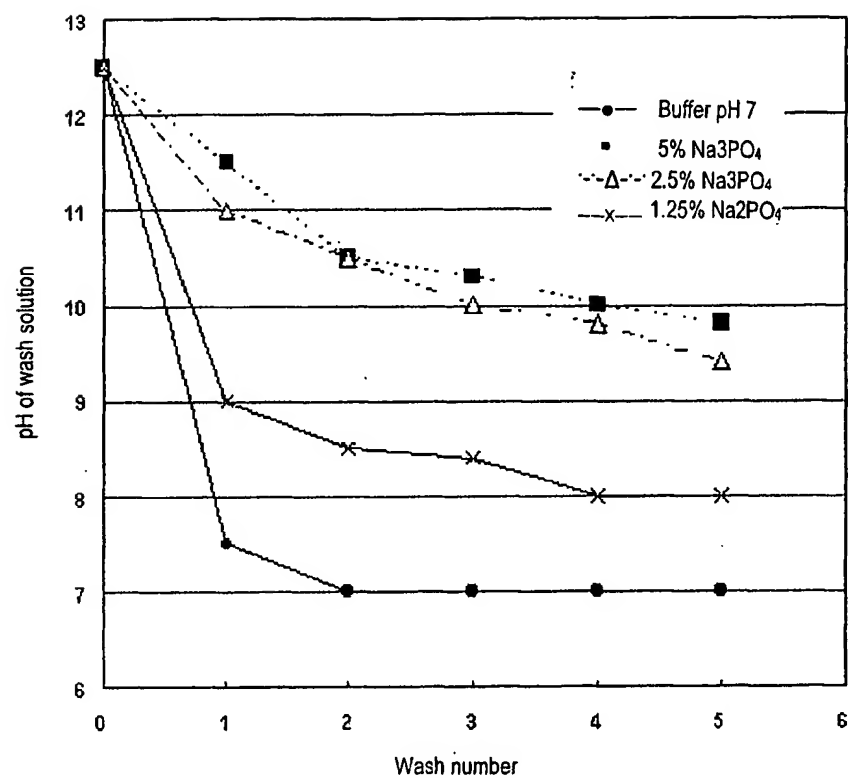


Figure 1

INTERNATIONAL SEARCH REPORT

International application No.

PCT/AU01/01370

A. CLASSIFICATION OF SUBJECT MATTER		
Int. Cl. ⁷ : A61K 51/06, A61P 35/00		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED		
Minimum documentation searched (classification system followed by classification symbols) Refer Electronic data base consulted below		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) File WPAT: IPC A61K 51/ , 43/ , 49/02, partic+ , microspher+ , glass, silic+ , ceram+ , polym+ , resin, styrene, coat+ , ferr+ , fe+ , magnet+ :		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	WO 200134196 A (Forschungszentrum Karlsruhe) 17 May 2001 Entire document	1-8, 13, 15, 16, 18, 20, 21, 23
X	US 4115536 A (Rothman, U.S.E. et al) 19 September 1978 Columns 1-12	1-8, 11-23
X	US 4108972 A (Dreyer, W.J.) 22 August 1978 Columns 1-14	1-11, 13, 15, 16, 18, 20, 21, 23
X	WO 8502772 A (Schroder, U et al) 4 July 1985 Pages 3-8	1-11, 13, 15, 16, 18, 20, 21, 23
<input type="checkbox"/> Further documents are listed in the continuation of Box C <input checked="" type="checkbox"/> See patent family annex		
* Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier application or patent but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family		
Date of the actual completion of the international search 23 November 2001		Date of mailing of the international search report 18 DEC 2001
Name and mailing address of the ISA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustalia.gov.au Facsimile No. (02) 6285 3929		Authorized officer G.J. McNEICE Telephone No : (02) 6283 2055

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/AU01/01370

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report			Patent Family Member		
WO	200134196	DE	19953636	DE	19953637
US	4115536	DE	2542255	FR	2285857
		JP	51061620	SE	7412164
US	4108972	NONE			
WO	8502772	DK	3770/85	EP	166755
		HK	1349/93	JP	9110727
		SE	8307060	SG	856/91
		US	5670135	US	5817291
		US	6203777	US	5720939
END OF ANNEX					